Managing Varicella Zoster Virus contact and infection in patients on anti-rheumatic therapy

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Short Title: Varicella Zoster Virus in the immunosuppressed

Abstract

Chickenpox and shingles can be more severe and occasionally life threatening in immunosuppressed patients. As such, some groups warrant a more detailed history, serological testing and consideration of prophylaxis following contact with the virus. Active disease may also require more aggressive treatment with antivirals. Guidance for the use of Varicella Zoster Immunoglobulin (VZIG) has recently been updated by Public Health England with important implications for rheumatology patients.

Key Words: Varicella Zoster Virus, VZV, varicella, chickenpox, zoster, shingles, immunosuppressed, varicella zoster immunoglobulin, VZIG, contact, infection, aciclovir, antiviral, vaccine

Key messages

Immunosuppressed patients should be assessed for prophylaxis following contact with Varicella Zoster Virus.

Some patients should have serological testing following contact even if they have a past history of chickenpox.

The chickenpox and shingles vaccines are live and should be avoided in some immunosuppressed groups.

Introduction

Varicella Zoster Virus (VZV) is one of eight herpesviruses that are known to cause disease in humans. Primary infection occurs as chickenpox, also known as varicella, with fever and widespread rash. In otherwise well children, it is self-limiting and rarely life threatening, although encephalitis and pneumonitis can complicate the disease. Primary infection in adults, whilst much less common, is more frequently associated with complications and has a 25-fold increased mortality compared to children [1]. Following primary infection, the virus lies dormant in the nervous system and can reactivate later in life as shingles, also known as zoster. Shingles may be complicated by chronic pain (post herpetic neuralgia) in the region affected, which occurs more frequently in older individuals [2]. Rarely, shingles can extend across multiple dermatomes, or even disseminate systemically. Some forms of immunosuppression increase the risk of both severe primary infection in people without prior exposure to the virus, and dissemination of infection following reactivation. This review will discuss the assessment and management of immunosuppressed adults with rheumatic disease who are at risk of VZV infection or reactivation.

Methodology

Publications included in this review were identified using computerised searches of the following databases: MEDLINE, EMBASE and CENTRAL. Search terms included combinations of Varicella Zoster Virus, VZV, chickenpox, shingles, immunosupp*, immunocomprom*, vaccin* VZIG, aciclovir/acyclovir, antiviral*, treatment, prevention with individual names of rheumatic conditions and treatments. Guidelines from Public Health England, Centre for Disease Control and other organisations were reviewed.

CASE SCENARIO

A 36 year-old woman, Mrs L is being treated with cyclophosphamide infusions and prednisolone 40mg daily for a small vessel vasculitis and asks for advice as her 3 year-old child has developed chickenpox. She believes she had chickenpox as a child.

Pathogenesis

There are nine genotype strains of VZV, although for clinical purposes, the virus is considered to be a single entity as cross-protection of immunity occurs. The virus is highly contagious with transmission starting one to two days prior to the onset of rash and continuing until all lesions have crusted over. Viral spread is from skin vesicles and respiratory droplets (Fig.1 from [3]). Primary VZV infection begins with replication in epithelial cells of the upper respiratory tract. The innate immune system mediates the first response via natural killer (NK) cells and the cytokines interferon IFN-α and IFN-γ [4]. During an incubation period of 10-21 days the virus spreads to local lymphoid tissue, T cells [3] and then the skin culminating in the characteristic widespread vesicular rash of chickenpox [5]. The cellular immune system, including CD4+ T-cells, then clears the virus and prevents life-threatening dissemination [6, 7]. Antibody responses are less important in primary infection, although have a role in neutralising the virus upon re-exposure [8].

During primary infection the virus establishes latency in dorsal root ganglia with later reactivation and anterograde transport to the skin causing the dermatomal eruption of shingles. Varicella specific T-cells are important in preventing shingles and their decline in number with advancing age correlates with an increasing incidence of disease [9].

Varicella DNA can be detected in blood from patients with shingles [10] and satellite lesions are an independent risk factor for severe disease [11]. A patient has disseminated zoster when twenty or more vesicles are present beyond the primary or adjacent dermatome [12], or in any patient with shingles and other organ involvement.

Epidemiology of infection and immunity

In the United Kingdom, where childhood vaccination against chickenpox is not routine, 77% of children experience the disease by the age of 5 [13]. By 16 years of age, 90% of the UK population will have serological evidence of exposure [14]. Infection may be subclinical and unrecognized by the individual: in adolescents with a negative or uncertain history of chickenpox, 67% and 84% show immunity respectively [15].

When someone in a household develops chickenpox, over two thirds of susceptible contacts will also develop primary infection [16]. In contrast, household contact with shingles, which has a lower total cutaneous viral load, results in chickenpox in an estimated 8-15% of susceptible individuals [17].

In the UK, the life time risk of shingles is 50% in those living to 85 years [18]. The adjusted risk increases with age and conditions including rheumatoid arthritis (RA) (table 1 from [19]). Immunosuppressive therapies may increase the risk and severity of chickenpox and shingles but establishing the degree of this risk for individual treatments is challenging. First, susceptibility to shingles is increased (regardless of treatment) in those with autoimmune conditions including RA

[19] and systemic lupus erythematosus (SLE) [20]. Second, chickenpox is rare in adults so available data is often limited to case reports or series with reporting and other biases. Third, incidence rates of shingles, although higher, are often not high enough to allow a meaningful comparison between groups in randomised controlled trials (RCTs). Therefore, our understanding of risk is often limited to data from retrospective or observational studies and registries where multiple factors, including other immunosuppressive medications, can confound results.

Nevertheless, the available evidence from the paediatric literature is strong for a temporal relationship between severe VZV infection and steroid use [21, 22]. In adults with RA, the adjusted hazard ratio (HR) for shingles in those taking prednisolone <7.5mg daily is estimated at 1.55 (95% CI 1.25–1.93) and 2.35 (1.81–3.04) for >7.5mg daily [23]. In contrast, data are not convincing for an increased risk of shingles or chickenpox in adults taking methotrexate [24] (and reviewed in [25]). A large prospective study of rheumatology patients in the U.S. found an increased risk of shingles in those taking cyclophosphamide (hazard ratio (HR) 4.2, 95% CI 1.6-11.5), azathioprine (HR 2 95% CI 1.2-2.3) or leflunomide (HR 1.4 95% CI 1.1-1.8) [26]. Data from a small series of paediatric renal transplant recipients have raised concern over the role of mycophenolate mofetil (MMF) in disseminated VZV infection [27].

Biologic therapies have now become a mainstay of treatment in many rheumatic diseases. A meta-analysis of patients with RA from registry data found an increased risk for shingles with anti TNF treatment as a class with an estimated hazard ratio of 1.6 (95% CI 1.16-2.23) [28]. Some data suggest a lower risk for etanercept [26, 29, 30]. A large prospective cohort study found no additional risk of HZ in patients taking anti TNF compared to conventional DMARD therapy [31]. A recent meta-analysis of 18 RCTs also found no significant increased risk of shingles in those taking anti TNF therapy compared to controls although the number of cases of shingles in all groups was small and many RCTs excluded patients at highest risk for example those over 75 [32]. In summary, registry data support a modest increased risk of shingles with anti TNF treatment whilst RCT data do not.

Data on other biologics are limited but two studies of patients with RA found no significant difference in adjusted hazard ratios of shingles in those taking abatacept, rituximab, tociluzimab and various anti TNF therapies [23, 33]. Preliminary data from phase II and III randomised controlled trials of the Janus Kinase (JAK) inhibitor tofacitinib in RA have shown an increased risk of uncomplicated zoster [34], recently estimated as double that of other biologics [35].

The specific effect of different immunosuppressive treatments on VZV humoral immunity is unknown. One study found that 17% of children lost detectable VZV IgG following chemotherapy for haematological and solid organ tumours [36]. Another found reduced cell mediated but not humoral immunity in adults with SLE and granulomatosis with polyangitis (GPA) on treatments including prednisolone, methotrexate, azathioprine and mycophenolate compared to healthy controls [37]. In an Israeli cross-sectional study of 104 adult patients with inflammatory bowel disease and a positive history of VZV infection or vaccination, 7 tested negative or equivocal for VZV IgG [38]. Of these, 6 were using anti TNF therapy and one methotrexate monotherapy.

The lifetime risk of contact with VZV in adult immunosuppressed rheumatology patients is also unknown but is likely to be significant given the typical longevity of treatment and particularly in those who have frequent contact with young children. Most immunosuppressed adult patients who come into contact with VZV have prior immunity but it is important to identify and consider treatment in those who do not, following significant exposure.

Assessment of VZV exposure and risk

Public health England (PHE) define significant exposure in the UK Immunisation Against Infectious Disease guide (also known as the Green Book) [39] as household contact, face-to-face contact (e.g. having a conversation), being in the same room for 15 minutes or the same 2 to 4 bed hospital bay with someone with chickenpox or exposed (e.g. ophthalmic) zoster. In general, non-household

contact with someone with covered shingles is not considered significant unless the person with shingles is themselves immunosuppressed and therefore considered to shed more virus. Contact with a well person within the two days prior to the onset of their chickenpox rash should also be considered significant if the above criteria are met.

Recent guidance from PHE [40] on the issuing of VZIG, divides immunosuppressed individuals into groups according to the nature of the immunosuppressive therapy. An interpretation of this division relevant to patients with rheumatic conditions is given in table 2 and the associated treatment algorithm (fig 2).

Public Health England advise that no further action is required following contact with VZV for patients in the low risk group. This is based on the assumed low risk of severe disease posed by these medications and the high likelihood of prior immunity even with a negative history of chickenpox. However, PHE also advise that aciclovir prophylaxis may be considered after discussion with the specialist physician caring for the patient. Some patients within this group will be at a higher risk than others so it may be prudent to establish a history of prior infection, vaccination or serology in, for example, someone on both prednisolone 20mg daily and azathioprine 3mg/kg despite them being in the lowest risk group.

If patients in the intermediate risk group A have a history of chickenpox, shingles, previous varicella/zoster vaccination or previous serological evidence of immunity, then no further immediate action is needed following contact with VZV. If not then serostatus should be established and VZIG) offered if seronegative (see next section). If testing were to delay treatment beyond 7 days post contact then the patient's age needs to be considered. Those over 50 are considered more likely to be immune so delaying treatment is acceptable; for those under 50, treatment should not be delayed beyond 7 days post contact whilst awaiting serological results. If a delay does occur then VZIG should still be considered up to 14 days post exposure when it is still potentially protective.

Individuals in the high risk group B include those on cyclophosphamide, cyclosporin, leflunomide, monoclonal antibodies or cytokine inhibitors. Following contact, patients in this group should have their serostatus rechecked regardless of a history of prior infection, vaccination or previous positive serology. The rationale being that immunosuppressive treatments in this group may deplete VZV specific antibody titres to non-protective levels. This recommendation is based on expert opinion as the impact of specific immunosuppressive regimens on VZV specific humoral and cellular immunity is largely unknown (see epidemiology section). Further, it is debatable whether some treatments including leflunomide should be included in this group on the available evidence [26].

Serological testing for VZV IgG is relatively low cost and results can be generally available within 24 hours. Varicella specific IgG will be detectable in most patients who have had chickenpox, shingles or received the varicella or shingles vaccine. However, commercial assays are less sensitive for detecting vaccine-induced immunity [41]. Serological assays may detect IgG in those who have recently received antibody containing blood products, such as human normal immunoglobulin (IVIG) [42], or after blood transfusion [43] –these are false positive with respect to identifying a past history of infection but are likely to reflect equivalent passive protection afforded by use of VZIG.

If a patient has existing immunity then no specific action is required following contact with VZV; however reports do exist of disseminated infection following exposure in this setting [44] and so patients should still be advised to urgently report early signs of infection.

Management of varicella exposure

Following significant contact with VZV, prophylaxis can be offered in two forms: antiviral agents (e.g. aciclovir or valaciclovir) and varicella zoster immunoglobulin (VZIG). There have been no RCTs directly comparing these modalities.

VZIG is prepared from pooled plasma of donors with suitably high titres of VZ antibody. The similar, but no longer available, zoster immune globulin (ZIG) was demonstrated to prevent chickenpox in healthy children when given within 72 hours of household exposure[45]. In immunocompromised children, ZIG [46, 47] and VZIG [48] reduce the incidence of chickenpox and modify disease severity compared to historical controls. The duration of protection that is provided after VZIG administration is unknown but is likely to broadly equate to the half-life of other immunoglobulins of 3-4 weeks [49]. Approximately half of susceptible household contacts will develop chickenpox despite receiving VZIG [50]. This group will generally have attenuated disease but should still be considered for antiviral therapy if a chickenpox like illness develops.

VZIG is given as an intramuscular (IM) injection. In patients for whom IM injections are contraindicated, for example those with clotting disorders or severe thrombocytopenia, IVIG (which will contain some VZV specific antibody) can be used [39]. In patients receiving regular (e.g. monthly) IVIG for gammaglobulin deficiencies, VZIG need not be used [39]. In patients taking warfarin, small volume IM injections (e.g. influenza vaccine) appear to be safe [51, 52]; it is not known if larger volume injections such as VZIG carry a significant risk. Options therefore include splitting the dose between different sites or giving it subcutaneously as per manufacturer guidance [49] although evidence of clinical efficacy via this route is lacking. Data regarding newer oral anticoagulants are also lacking.

If VZIG and IVIG are unavailable, contraindicated or a patient prefers not to receive a blood-derived product, aciclovir can be used prophylactically at a dose of 10mg/kg 4 times a day for 7 days, starting 1 week after exposure [40, 53]. Aciclovir prevents the development of chickenpox following close contact in healthy, susceptible children but there is some concern that it may attenuate long term immunity [54]. One small study has suggested added benefit of aciclovir with VZIG compared to VZIG alone in children with renal disease taking steroids [55].

In patients who meet criteria for receiving VZIG, it is reasonable to withhold biologic therapy until the incubation period of 21 days has passed. This is in keeping with manufacturer guidance for Etanercept. Sulfasalazine and hydroxychloroquine are generally considered to be of low risk in this setting but decisions to withhold other non-biologic DMARDs must be assessed on an individual basis. It is noteworthy that there is an increased risk of neurotoxicity if ciclosporin is co-administered with aciclovir or valaciclovir [56] . Aciclovir is excreted by the same renal tubular system as mycophenolate mofefil but co-administration does not result in clinically significant change in drug levels in patients with normal renal function [57].

Primary prevention

A single dose, live attenuated chickenpox vaccine was licensed and recommended for routine use in children in the U.S. in 1995. The schedule was changed in 2005 to two doses given at least four weeks apart following evidence that this regimen provides 98% protection against clinical disease in children over a period of 10 years, compared to 94% following a single dose [58]. Seroconversion rates in healthy adolescents and adults are approximately 75% and 99% after one or two doses respectively [59].

In the UK, the chickenpox vaccine is currently recommended only for non-immune healthcare workers and for non-immune close contacts of more severely immunocompromised patients [60] such as those receiving chemotherapy. This approach could be extended, for example, to a non-immune child of a mother receiving cyclophosphamide and high dose steroids for a rheumatological condition.

The chickenpox vaccine is associated with a mild vesicular rash in 8% of healthy seronegative adults [61]. Concern over vaccine-strain disease has led PHE to advise against the use of the vaccine in immunosuppressed patients [39]. A recent study found that when given to 31 non-immune children

receiving active chemotherapy for haematological or solid organ malignancy, the vaccine caused only a mild vesicular rash in 7 [62]. The risk of vaccination in seronegative, immunosuppressed adults is unknown. The Centre for Disease Control (CDC) advise avoidance in those who are severely immunosuppressed including those taking more than 20mg of prednisolone daily for more than two weeks. Guidance from EULAR states the vaccine can be used in those mildly immunosuppressed, but without defining this group [63].

Public Health England do allow for the use of the more potent, live zoster vaccine in those taking long term prednisolone <20mg per day and/or methotrexate <25mg per week or azathioprine <3mg/kg/day [64]. This may seem paradoxical given the zoster vaccine contains 14 times more virus than the chickenpox vaccine but this might reflect that the guidance for the latter was written with more heavily immunosuppressed paediatric patients in mind. Further, it is generally assumed that patients receiving the zoster vaccine will have prior immunity and therefore be at lower risk of vaccine strain disease. Despite this, PHE do not explicitly prohibit its use in immunosuppressed patients who are seronegative. In contrast, EULAR do recommend avoiding the zoster vaccine in this group [63] . The CDC do not require prior immunity to be established and state the vaccine may be considered even in patients on biologic therapy on a case by case basis [65]. If a decision is made to vaccinate a patient known to be seronegative, then expert opinion suggests the lower potency chickenpox vaccine should be used [66]. There are case reports of fatal vaccine strain disease following inadvertent zoster vaccination in patients who are heavily immunosuppressed [67]. However a recent retrospective study in the U.S. found no cases of serious vaccine strain disease in 4826 patients receiving various immunosuppressive medications including high dose steroids (550 patients), methotrexate (683), azathioprine (164), leflunomide (126) and etanercept (130) [68]. It is not known how many of these patients had prior immunity but in keeping with the rest of the U.S. population it is likely to be in the region of 99%, compared to 90% in the UK [14, 69]. A randomised controlled pilot study assessing the safety and effectiveness of the live zoster vaccine in patients on anti-TNF therapy is currently recruiting [70].

If an adult immunosuppressed patient does develop a vesicular rash following vaccination, viral swabs should be sent for genomic analysis to distinguish vaccine strain from wild-type virus.(see [71]).

An inactive, herpes zoster subunit vaccine, given intramuscularly 2 months apart, has recently been trialled in healthy, non-immunosuppressed adults. In those over 50, the vaccine is 97% effective in preventing HZ over a mean follow up of 3.2 years [72]. In patients over 70 the vaccine is 90% effective over 3.7 years with a similar reduction in post herpetic neuralgia [73]. Immunosuppressed patients were excluded from both studies.

An alternative, heat inactivated VZV vaccine, given as four separate doses 30 days apart reduces the incidence of zoster in patients receiving bone marrow transplantation for lymphoma [74]. The vaccine is immunogenic in various immunosuppressed groups [75] and a large placebo controlled, phase III trial assessing clinical efficacy in these groups is due to publish soon [76].

If a non-live vaccine becomes available and is effective in immunosuppressed patients, it will remove much of the uncertainty described above and may play an important role in both primary prevention and post-exposure prophylaxis. Until then, the live varicella vaccine may be considered prior to immunosuppression in some groups who have no history of chickenpox, shingles or vaccination and are found to be seronegative. However, following PHE guidance, this would necessitate a delay in treatment of at least 2 or 6 weeks if a single or double dose regimen is used respectively.

Treatment of active disease

Aciclovir reduces the severity of chickenpox in healthy children [77] and also in adults when given within 24 hours of disease onset [78] [79]. The British Infection Society recommends treatment of chickenpox in immunocompetent adults (without complications) with oral antivirals within 24-48 hours of rash onset [80]. Immunosuppressed patients should receive IV aciclovir 10mg/kg three

times daily (if eGFR is above 50). The society defines immunosuppressed as including patients in the equivalent of PHE groups A and B (see above) but also those taking methotrexate or azathioprine. It was issued before much of the reassuring safety data regarding methotrexate was published [24].

In the context of shingles, aciclovir administered within 48-72 hours of rash onset significantly reduces the incidence of acute neuritis in healthy adults [81] although there may not be any associated reduction in chronic post herpetic neuralgia [82]. Valaciclovir is an alternative antiviral agent with a longer, more convenient dosing interval and it may be more effective than aciclovir in treating shingles [83]. In the immunosuppressed, particularly in those taking high dose steroids and/or biologic therapies, antivirals should be initiated if vesicles or active lesions are present, regardless of time since onset [84, 85]. Treatment should be continued for at least 7 days and until all lesions have crusted over and no new lesions have appeared for 48 hours.

Conclusion

Varicella zoster virus infection is common. Most, but not all, people in the United Kingdom are exposed to the virus in childhood. For those who are not and who subsequently commence immunosuppressive therapy, rheumatologists need to be aware of the risk of severe de novo infection and the indications for VZIG following a significant contact. Ideally, non-immune patients should receive the chickenpox vaccine prior to starting immuosuppressive therapy. Available evidence suggests the higher potency shingles vaccine is largely safe in all but the severely immunosuppressed. However, uncertainty remains about how exactly to define this group and the necessity of establishing serostatus prior to administration. If effective, an inactivate vaccine will make these concerns less relevant [72, 75]. Immunosuppressed patients who develop uncomplicated shingles should be treated with oral antiviral therapy. Immunosuppressed patients with chickenpox or disseminated, multidermal or ophthalmic zoster should be admitted for IV antiviral therapy with appropriate infection control measures.

Mrs L should be tested for VZV IgG to establish whether she has immunity as despite her history of chickenpox she falls into the high risk PHE group B. She tests negative and should therefore be offered VZIG. She should be advised to watch for a vesicular rash and antivirals started promptly if one develops. The live varicella vaccine for post exposure prophylaxis would be contraindicated given her degree of immunosuppression. If she has other children who have not had chickenpox they should be considered for the live varicella vaccine. Should an inactivated VZV vaccine become available she would be a good candidate to receive it once the protective effects of VZIG have worn off.

Future research questions and outstanding controversy

A number of outstanding questions remain including: What is the effect of different immunosuppressive medications on VZV specific cell mediated and humoral immunity over time? Can we better define which patients will benefit most from serological testing and prophylaxis following contact with VZV? Is VZIG more or less effective than aciclovir as post exposure prophylaxis and when should they be combined? Who should have their immunosuppressive treatment delayed to allow vaccination? Is delaying low risk immunosuppression necessary in the context of receiving the live chickenpox vaccine and does it affect the likelihood of seroconversion? Which patients should have their serostatus checked prior to receiving the higher dose live shingles vaccine? If an inactivated vaccine becomes available, who should receive it? Should it be included as part of post-exposure prophylaxis and what is the optimum timing of administration?

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Figure 1. Varicella Zoster Virus life cycle

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Figure 2. Algorithm for approach following reported contact with Varicella Zoster Virus in an immunosuppressed patient

Derived from PHE guidance for issuing VZIG (Oct 2016).

Table 1. Estimated rate of zoster patients with various risk factors, by age group

Key risk factors of interest	Rate of zoster/1000 person years (99% CI)			
	<50 years	50-59 years	60-69 years	≥70 years
General population (2010)	2.08 (1.74 to 2.49)	4.37 (3.72 to 5.12)	6.69 (5.76 to 7.76)	8.84 (7.49 to 10.43)
Rheumatoid arthritis	3.51 (2.40 to 5.13)	6.35 (3.46 to 11.66)	9.96 (5.57 to 17.77)	12.47 (6.94 to 22.41)
Systemic lupus erythematosus	6.32 (3.73 to 10.74)	8.67 (3.2 to 23.46)	8.20 (2.99 to 22.45)	11.36 (4.22 to 30.60)
Inflammatory bowel disease	3.59 (2.56 to 5.04)	6.13 (3.55 to 10.58)	8.67 (5.10 to 14.74)	10.41 (6.10 to 17.74)
Chronic obstructive pulmonary disease	2.31 (1.40 to 3.84)	5.62 (2.44 to 12.94)	9.19 (4.09 to 20.62)	11.54 (5.08 to 26.20)
Asthma	2.58 (2.03 to 3.28)	5.20 (3.81 to 7.11)	8.16 (6.04 to 11.00)	10.44 (7.64 to 14.25)
Chronic Kidney disease	3.39 (2.38 to 4.85)	5.51 (3.17 to 9.59)	7.60 (4.52 to 12.78)	9.70 (5.74 to 16.37)
Depression	2.59 (2.03 to 3.31)	4.89 (3.51 to 6.80)	7.22 (5.19 to 10.05)	9.71 (6.94 to 13.58)
Diabetes	2.66 (1.99 to 3.56)	4.84 (3.23 to 7.27)	6.79 (4.62 to 9.97)	8.55 (5.76 to 12.70)
Type 1	3.14 (2.14 to 4.67)	5.08 (2.32 to 11.16)	6.55 (2.66 to 16.12)	5.49 (1.75 to 17.21)
Type 2	2.54 (1.84 to 3.54)	4.77 (2.93 to 7.78)	6.79 (4.25 to 10.84)	8.54 (5.28 to 13.79)

Reproduced from Forbes HJ et al. Quantification of risk factors for herpes zoster: population based case-control study. BMJ 2014; 348:g2911

Table 2. Immunosuppressive risk of Varicella Zoster Virus infection with different medications, inferred from guidance from Public Health England

Low Risk	Intermediate Risk (PHE group A)	High Risk (PHE group B)
Prednisolone, methotrexate or azathioprine at doses lower than in group A Sulfasalazine hydroxychloroquine	Any of following in last 3 months: Prednisolone >40mg per day for > 1 week OR >20mg per day for >2 weeks Methotrexate >25mg/week Azathioprine >3mg/kg/day Mercaptopurine 1.5mg/kg/day	Any of following in last 6 months: Cyclophosphamide Biologics Cyclosporin Leflunomide

Adapted from Guidance for issuing Varicella Zoster Immunoglobulin [40].